CLAIMS

1. A method of activating a cell as a result of one type of extracellular interaction between said first cell and a molecule associated with a second target cell characterised in that said first cell is provided with a DNA delivery system comprising DNA coding for one or more recombinant chimeric receptors comprising two or more different cytoplasmic signalling components, wherein said cytoplasmic components are not naturally linked, and at least one is derived from a membrane spanning polypeptide.

2. A method according to Claim 1 wherein the cytoplasmic signalling components are capable of acting together cooperatively.

3. A method according to Claim 1 or Claim 2 wherein said DNA additionally codes for signal peptide, binding and/or transmembrane components of said one or more chimeric receptors, wherein the binding component is capable of recognising a cell surface molecule on a target cell.

4. A method according to Claim 3 wherein the signal peptide, transmembrane and cytoplasmic signalling components and all or part of the binding component are coded for by a single DNA coding sequence.

5. A method according to Claim 3 wherein each cytoplasmic signalling component is coded for by a separate DNA coding sequence, each of DNA sequence additionally coding for a signal peptide, a transmembrane component and all or part of a binding component.

6. A method according to Claim 4 or Claim 5 wherein said DNA codes for part of said binding component and an additional separate DNA coding sequence codes for the remainder of the binding component.

7. A method according to Claim 5 or Claim 6 wherein the binding component coded for by one DNA sequence is capable of

participating in the same type of extracellular binding event as the binding component coded for by any other DNA sequence.

8. A method according to Claim 7 wherein each binding component binds to the same molecule associated with the target cell.

9. A method according to Claim 8 wherein each binding component is the same.

10. A method according to any one of Claims 1 to 9 wherein the one or more recombinant chimeric receptors are capable of recognising a viral or cell surface molecule on a target cell.

11. A DNA delivery system comprising DNA in association with a carrier said DNA coding for a recombinant chimeric receptor capable of one type of extracellular interaction and comprising two or more different cytoplasmic signalling components which are not naturally linked, and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide.

12. A DNA delivery system comprising DNA in association with a carrier said DNA coding for two or more recombinant chimeric receptors each capable of the same one type of extracellular interaction and wherein each of said receptors comprises one or more different cytoplasmic signalling components which are not naturally linked, and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide.

13. A DNA delivery system according to Claim 11 wherein said DNA codes in reading frame for:

i) a signal peptide component;

ii) a binding component capable of recognising a cell surface molecule on a target cell;

iii) a transmembrane component;

iv) two or more different cytoplasmic signalling components which are not naturally linked, and wherein at least one of said cytoplasmic

components is derived from a membrane spanning polypeptide: and optionally

v) one or more spacer regions linking any two or more of said i) to iv) components.

14. A DNA delivery system according to Claim 11 wherein said DNA comprises 1) a first DNA which codes in reading frame for:

i) a signal peptide component;

ii) part of a binding component;

iii) a transmembrane component;

iv) two or more cytoplasmic signalling components which are not naturally linked. and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide: and optionally

v) one or more spacer regions linking any two or more of said i) to iv) components; and 2) a second separate DNA which codes in reading frame for a signal peptide component and a further part of the binding component ii) coded for by said first DNA, such that the binding component parts together are capable of recognising a cell surface molecule on a target cell.

15. A DNA delivery system according to Claim 12 wherein said DNA comprises a first and a second separate DNA each of which codes in reading frame for:

i) a signal peptide component;

ii) a binding component capable of recognising a cell surface molecule on a target cell;

iii) a transmembrane component:

iv) one or more different cytoplasmic signalling components which are not naturally linked. and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide: and optionally

v) one or more spacer regions linking any two or more of said i) to iv) components; provided that said first DNA codes for at least one signalling component iv) that is not coded for by said second DNA.

16. A DNA delivery system according to Claim 12 wherein said DNA comprises 1) a first and a second separate DNA each of which codes in reading frame for:

i) a signal peptide component;

ii) one part of a binding component;

iii) a transmembrane component;

iv) one or more different cytoplasmic signalling components which are not naturally linked, and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide; and optionally

v) one or more spacer regions linking any two or more of said i) to iv) components; provided that said first DNA codes for at least one signalling component iv) that is not coded for by said second DNA; and 2) a separate third and fourth DNA each of which codes in reading frame for a signal peptide component and a further part of the binding component ii) coded for by said first and second DNA respectively, such that the binding component parts together provided by the first and third DNA and together provided by t he second and fourth DNA are each capable of recognising a cell surface molecule on a target cell.

17. A DNA delivery system according to Claims 13 to 16 wherein each signal peptide component is an immunoglobulin signal sequence.

18. A DNA delivery system according to Claims 15 to 17 wherein the binding component coded for by said first DNA is the same as the binding component coded for by said second DNA.

19. A DNA delivery system according to Claims 13 to 18 wherein the binding component is an antibody or an antigen binding fragment thereof.

20. A DNA delivery system according to Claim 19 wherein the antibody or fragment thereof is an engineered human antibody or antigen binding fragment thereof.

21. A DNA delivery system according to Claims 18 to 20 wherein the binding component is a single chain Fv fragment.

22. A DNA delivery system according to Claims 18 to 20 wherein the binding component is a Fab' fragment.

23. A DNA delivery system according to any one of Claims 13 to 22 wherein the transmembrane component is derived from all or part of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD8, CD4, a cytokine receptor or a colony stimulating factor receptor.

24. A DNA delivery system according to Claim 23 wherein the transmembrane component is derived from all or part of CD28.

25. A DNA delivery system according to any one of Claims 11 to 24 wherein the cytoplasmic signalling components are capable of acting together cooperatively.

26. A DNA delivery system according to any one of Claims 13 to 25 wherein the cytoplasmic signalling components are derived from all or part of the cytoplasmic domains of a zeta, eta or epsilon chain of the T-cell receptor, CD28, the γ chain of a Fc receptor, a cytokine receptor, a colony stimulating factor receptor, a tyrosine kinase or an adhesion molecule, B29, MB-1, CD3 delta, CD3 gamma, CD5 or CD2.

27. A DNA delivery system according to Claim 26 wherein the cytoplasmic signalling components are ITAM containing cytoplasmic components.

28. A DNA delivery system according to Claim 26 or Claim 27 wherein the cytoplasmic signalling components are derived from all or part of CD28 and/or the zeta chain of the T-cell receptor.

29. A DNA delivery system according to any one of Claims 11 to 28 wherein the cytoplasmic signalling components are in any orientation relative to one another.

30. A DNA delivery system according to any one of Claims 13 to 29 wherein said DNA coding for components i) to iv) additionally codes for one or more spacer regions linking the binding component ii) and the transmembrane component iii).

31. A DNA delivery system according to Claim 30 wherein two or more different spacer regions link the binding component ii) and the transmembrane component iii), both regions either being coded for by one DNA sequence or when a first and second DNA sequence is present one region being coded for by said first DNA and the other different region being coded for by said second DNA.

32. A DNA delivery system according to Claims 30 or Claim 31 wherein the spacer region is selected to provide one or more free thiol groups.

33. A DNA delivery system according to Claims 30 to 32 wherein the spacer region is derived from all or part of the extracellular region of CD8, CD4 or CD28 .

34. A DNA delivery system according to Claims 30 or Claim 32 wherein the spacer region is all or part of an antibody constant region.

35. A DNA delivery system according to Claims 30 to 32 wherein the spacer region is derived from all or part of an antibody hinge region linked to all or part of the extracellular region of CD28.

36. A DNA delivery system according to any one of Claims 11 to 35 wherein the carrier is a viral vector or a non-viral vector.

37. A DNA delivery system according to Claim 36 wherein the non-viral vector is a liposomal vector.

38. A DNA delivery system according to Claim 37 wherein the carrier is a targeted non-viral vector.

39. A DNA delivery system according to Claim 38 wherein the targeted vector is an antibody targeted liposome.

40. A DNA delivery system according to Claim 38 wherein the targeted vector is an antibody targeted condensed DNA.

41. A DNA delivery system according to Claim 40 wherein the targeted vector is an antibody targeted protamine or polylysine condensed DNA.

42. A DNA delivery system according to Claim 38 wherein the targeted vector is antibody targeted naked DNA.

43. A DNA delivery system according to Claims 39 to 42 wherein the antibody is a whole antibody or an antigen binding fragment thereof.

44. A DNA delivery system according to Claim 43 wherein the antibody is an engineered human antibody or an antigen binding fragment thereof.

45. An effector cell transfected with a DNA delivery system according to any one of Claims 1 to 444.

46. An effector cell according to Claim 45 which is a lymphocyte, a dendritic cell, a B-cell, a haematopoietic stem cell, a macrophage, a monocyte or a NK cell.

47. An effector cell according to Claim 46 which is a cytotoxic T-lymphocyte.

48. A DNA delivery system according to any one of Claims 11 to 47 for use in the treatment of infectious disease, inflammatory disease.

cancer, allergic/atopic disease, congenital disease, dermatologic disease, neurologic disease, transplants and metabolic/idiopathic disease.

49. A DNA delivery system according to Claim 48 for use in the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, eczema, cystic fibrosis, sickle cell anaemia, psoriasis, multiple sclerosis, organ or tissue transplant rejection, graft-versus-host disease or diabetes.

50. A pharmaceutical composition comprising a DNA delivery system according to any one of Claims 11 to 44 together with one or more formulatory agents.

51. A pharmaceutical composition according to Claim 50 wherein the formulatory agent is a suspending, preservative, stabilising and/or dispersing agent.

52. DNA coding for a recombinant chimeric receptor for use in a delivery system according to any one of Claims 11 to 44.